Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 7321–7325
Tetrahedron

Organic reactions in supramolecular gel media: reaction driven release of reagents in a macrocyclisation reaction

Juan F. Miravet* and Beatriu Escuder*

Dpt. de Química Inorgànica i Orgànica, Universitat Jaume I, E-12071 Castelló, Spain

Received 13 November 2006; revised 25 January 2007; accepted 9 February 2007
Available online 20 February 2007

Abstract—A bifunctional reactive organogelator containing *p*-nitrophenyl carbamate moieties has been reacted with (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine to produce a L-valine derived macrocyclic bisurea. The macrocyclisation can be carried out very efficiently in the presence of the supramolecular gel formed by the biscarbamate, although the results indicate that the reaction takes place on the soluble species present in the system. The reversible nature of a supramolecular gel together with the high active surface of its fibrillar network permits the behaviour of the studied gel as an on-demand supplier of reagents to the solution phase.

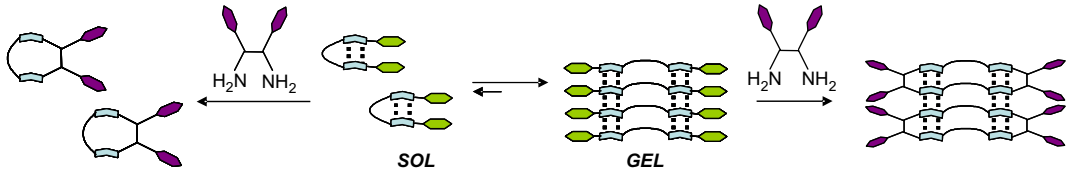
1. Introduction

Supramolecular gels, formed by the hierarchical self-assembly of low molecular weight organic compounds through non-covalent interactions, have received increasing attention in the last decade.[1,2] Applications have been reported in materials chemistry and drug delivery among others.[3] However, their use as media for organic transformations has received limited attention.[4]

We have recently shown that a reactive organogel can be prepared from compound **1** in acetonitrile.[5] This compound, bearing *p*-nitrophenyl carbamate fragments, easily reacts with amines in a diffusion-controlled process to give bisureas. We already noticed in preliminary studies with a bisfunctional amine, ethylenediamine, that the proportion of the different oligomeric products was different when the reaction was carried out in the presence of the gel compared with the presence of refluxing solvent. We observed a lower degree of oligomerisation and a higher amount of 1+1 and 2+2 cyclic products when the reaction was carried out in the gel state at room temperature.

Synthetic macrocycles, and in particular amino acid derived structures, have received much attention in the recent years.[6] The fascinating properties of their natural counterparts have pushed forward research in this field and different methodologies have been applied for their synthesis, such as high-dilution strategies, reagent preorganisation or guest templating among others.[7]

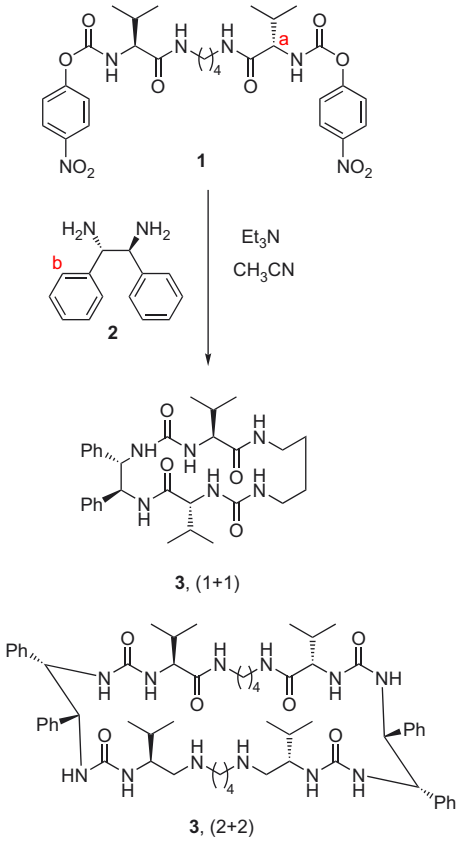
In this context and following our previous research in this field, we envisaged the opportunity of studying whether the self-assembled one-dimensional aggregates of a supramolecular gel could act as a template for a macrocyclisation reaction (see Scheme 1). For this purpose, we have studied the reaction of the reported gel of compound **1** in acetonitrile with (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine (**2**) (Scheme 2). This diamine, less flexible than ethylenediamine used in our previous studies, has been chosen in order to minimise intercolumnar cross-reaction and to favour (2+2)



Scheme 1.

* Corresponding authors. Tel.: +34 964728235; fax: +34 964728214; e-mail: escuder@qio.uji.es

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.02.069



Scheme 2.

intracolumnar reaction. In addition, the phenyl rings increase solubility of the products allowing easy purification.

2. Results and discussion

Compound **1** was synthesised as described previously.[5] The self-assembly and structural features of compound **1** were then analysed in detail. For this purpose, spectroscopic techniques and molecular modelling have been used as reported before for other analogues.[8]

When gelation was monitored by FTIR it was observed that stretching vibrations of non-associated carbamate and amide groups (1751 and 1679 cm^{-1}, respectively) simultaneously decreased over time whereas a new band corresponding to associated carbamate C═O stretching appeared at 1716 cm^{-1} (Fig. 1). The associated amide C═O band could not be observed due to overlapping with solvent signals. This suggests that both amide and carbamate groups are involved in intermolecular H-bonding during gelation. Furthermore, the study of the CH_2 asymmetric and symmetric stretching vibration bands in the xerogel of compound **1** suggests some extent of folding of the butylenic spacer since no signals at low frequencies, commonly assigned to all-trans extended conformations, were observed.

NMR studies of compound **1** were carried out in [D_3]acetonitrile for both diluted and gel samples (concentrations were 0.5 mM and 5 mM, respectively). The chemical shift value of the signals observed for both systems was identical in

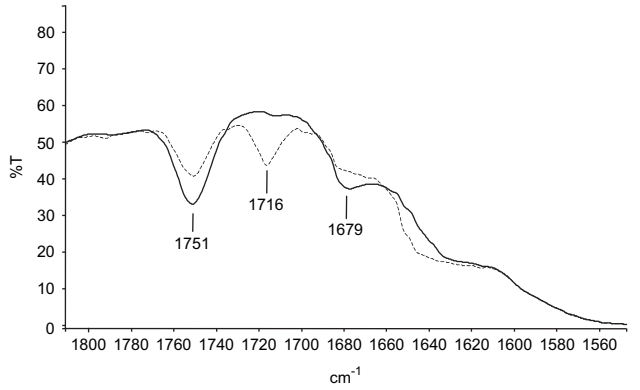


Figure 1. FTIR C═O stretching region of compound **1** in acetonitrile before (solid line) and after gelation (dashed line).

accordance with the fact that in the gel samples only free gelator molecules are observed by NMR.[9,10] In the case of gel samples, negative NOEs associated to a transfer-NOE mechanism can be observed, which indicates that an exchange of gelator molecules from solution to gel phase is taking place. According to the fundamentals of transfer-NOE, this exchange process is fast in the scale of relaxation times and reveals the dynamic nature of the system (Fig. 2).

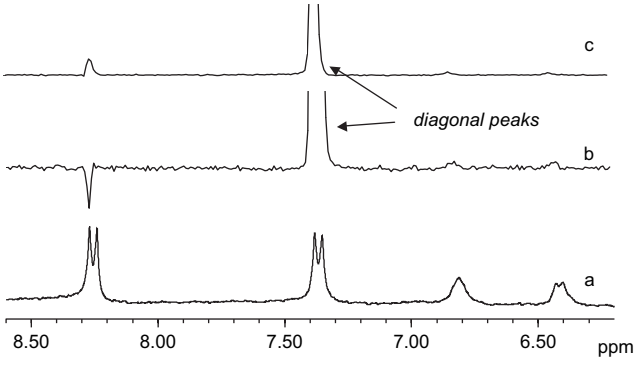


Figure 2. Partial NMR spectra of **1** in CD_3CN (30 °C, 500 MHz). (a) Spectrum of a gel (5 mM). (b) Trace of NOESY spectrum obtained for a 0.5 mM dissolution. (c) Trace of NOESY spectrum obtained for a gel (0.5 mM).

In order to evaluate the possible presence of folded conformations of **1** in solution as a result of intramolecular H-bonding, the NMR of compound **4** was studied in [D_3]acetonitrile (Fig. 3). This compound is an analogue of **1** that contains only one L-valine unit and, therefore, intramolecular H-bonding is precluded for this molecule. The comparison of

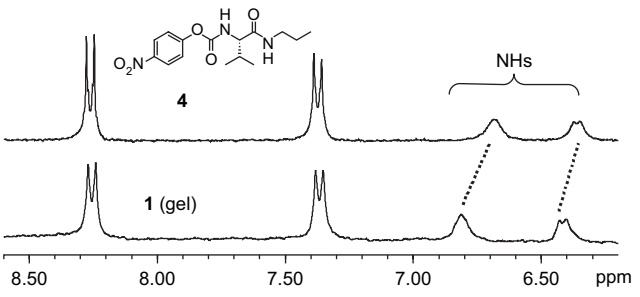


Figure 3. Partial ^1H NMR spectra of the gel (5 mM) formed by compound **1** (bottom) and of a 5 mM solution of compound **4** in CD_3CN (top). Signal intensities are normalised for comparison.

chemical shifts of NH groups for diluted samples reveals that the signals of **1** are shifted downfield when compared to those of **4**. This effect is not as pronounced as that described for related systems, but suggests that intramolecular H-bonding may be present in the structure of **1** in solution.

On the other hand, Figure 4 shows the low energy structures found for a conformational search for compound **1**. As can be seen, for compound **1** both extended (A) and folded (B) conformations were found as the two most stable forms within an interval of 3 kcal/mol. In the case of the folded conformer, intramolecular H-bonding between the amide carbonyl and amide and carbamate NHs is responsible for the stabilization of this conformer.

For the study of the reaction between the gel formed by **1** and diamine **2**, in a typical experiment, the gel was formed by dissolving compound **1** in hot CH_3CN followed by slow cooling at room temperature. After few hours a mixture of 1 equiv of compound **2** and 2 equiv of Et_3N in CH_3CN was added on top of the gel. The mixture was slightly shaken to favour diffusion and reaction started immediately as could be seen by the appearance of yellow colour from *p*-nitrophenolate anion. The reaction was left overnight and at this point the gel was completely disassembled, in contrast to the reaction reported previously with ethylenediamine. Afterwards the insoluble material present in the reaction mixture was filtered and washed consecutively with base, water and Et_2O. The crude of reaction product was analysed by ^1H NMR and mass spectrometry. The main MS peak was found to be a (1+1) cyclic component ($[M+Na]^+$, 573.5 *m*/*z*) with a small peak corresponding to a (2+2) cycle ($[M+Na]^+$, 1123.8 *m*/*z*). The first was isolated by chromatography corresponding to a 78% yield (identity was confirmed by ^1H and ^{13}C NMR and MS, see Section 4). Surprisingly, the (2+2) cycle, which may have been predicted to derive from a gel template effect, was not the major product of the reaction.

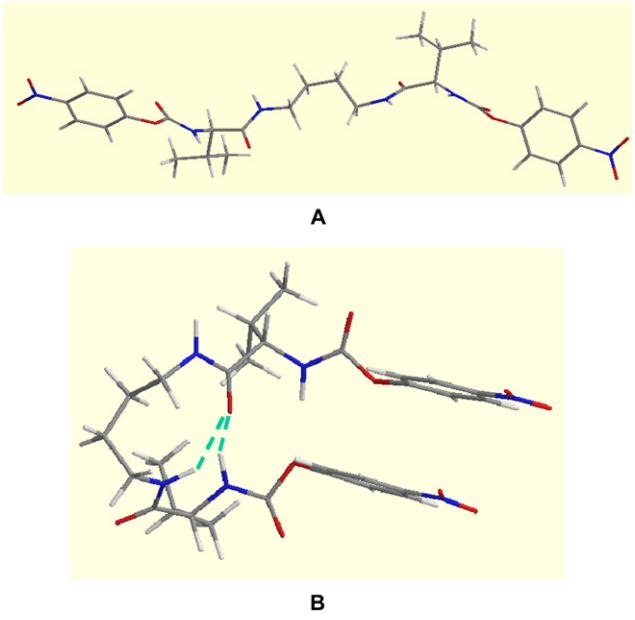


Figure 4. Lowest energy conformations found for compound **1** (MACROMODEL 7.0, AMBER*, $CHCl_3$).

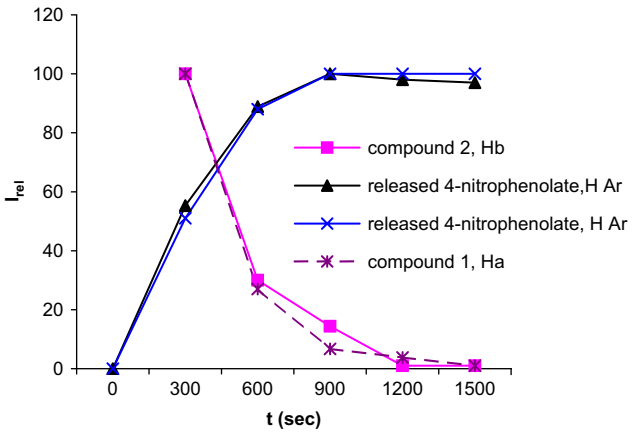


Figure 5. NMR kinetic profile of reaction between compound **1** and diamine **2** in CD_3CN (see Scheme 2 for numbering of signals).

In order to gain further insight into this process, the reaction in the gel phase at room temperature was performed in [D_3]acetonitrile and monitored by ^1H NMR. As mentioned previously, ^1H NMR of the starting gel only shows the signals corresponding to the fraction of compound **1** in solution since the aggregated molecules have short transversal relaxation times and are ^1H NMR silent.[10] A mixture of Et_3N and diamine **2** dissolved in 50 μL of solvent was added and, after slight shaking, spectra were taken at different times. The reaction was almost complete after 15 min as the intensity of signals corresponding to released 4-nitrophenolate (**5**) reached a plateau (Fig. 5).

All these data raise a fundamental question that appeared in our previous studies on compound **1**: is the reaction occurring in the gel or the sol phase? As shown for example by NMR studies (see above), a supramolecular gel is a dynamic system in which the assembly equilibrium, at the minimum gel concentration, is shifted to the gel phase. However, it is expected that if gelator was consumed in solution faster than in the aggregated form, gelator molecules would be continuously released to the solution in order to restore the equilibrium and in this way, most of the molecules would react in a non-aggregated form.

It can be deduced from the kinetic profiles of the α-proton in compound **1** remaining in solution and the aromatic protons of diamine **2** that both reagents are consumed following a similar rate profile (Fig. 5). All this seems to indicate that reaction is taking place either simultaneously in both gel and sol phases or as fast as the disassembly of the gel into monomer units. Moreover, the appearance of products could not be detected by ^1H NMR since these immediately aggregate and separate as a suspension.

In order to study the effect of the gel in the observed reactivity further experiments were proposed in which the reaction was carried out in slightly different conditions: (i) similar conditions as for the gel experiment but in refluxing acetonitrile, (ii) at room temperature, with a concentration of compound **1** equivalent to that of the sol phase that coexists with the gel and (iii) idem in refluxing acetonitrile. Reaction crudes were analysed by MS and yields calculated after chromatographic purification are collected in Table 1.

Table 1. Results of reactions between **1** and diamine **2**

Starting sample	Total concentration of compound **1** (mM)	Temperature	Yield (1+1) (%)
Gel	5	rt	78
Diluted	0.5	rt	72
Gel	5	Reflux	34
Diluted	0.5	Reflux	30

As can be seen, similar yields were obtained at room temperature for both gel and diluted sol systems. So, the presence of the gel appears to have no effect on the product distribution. On the other hand, a decrease of the (1+1) cycle yield with temperature is observed for both concentrations. This could be due to an increase in both molecular and conformational mobility of compound **1** at higher temperature, which provoked a decrease of the preorganisation and favoured molecular collisions, leading to the formation of oligomers as detected by MS of the crude of reaction.

At this point, collecting all the experimental evidence, it seems reasonable to propose that partial folding could allow proximity of both ends of the molecule during the reaction facilitating (1+1) cyclization. As previously described for related bolaamphiphilic carbamates, compound **1** forms a gel by assembling in an adaptable extended sheet-like structure via intermolecular H-bonding. However in solution the flexible butylenic spacer allows folding by intramolecular H-bonding.[7]

Molecular mechanics calculations were also performed on a hypothetical model intermediate compound (**5**) and it could be observed that, when one of the terminal 4-nitrophenyloxy groups of compound **1** was replaced by fragment **2**, the conformational search quickly converged into a folded global minimum conformation (Fig. 6).

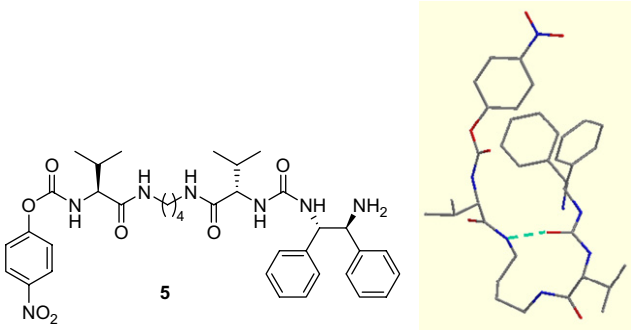


Figure 6. Lowest energy conformation found for model compound **5** (MACROMODEL 7.0, AMBER*, $CHCl_3$).

3. Conclusion

In summary, it seems that in this reaction, the main role of the gel formed by **1** is to act like a separated phase in a saturated solution that releases its components when the concentration of soluble species is decreased by reaction, according to a precipitation/gelation equilibrium constant (Scheme 2). In other words, the studied supramolecular gel can be considered as a controlled release system of reactive fragments in solution acting as an 'on-demand' injection system. This behaviour can be of interest for a number of synthetic applications due to the fact that the release of reagent provided by the supramolecular gel avoids the use of large quantities of solvent and keeps the concentration of soluble species almost constant during all the reaction process. These properties could be especially useful for reactions requiring a precise pre-determined concentration value to work properly, as is the case for high-dilution macrocyclisations. It has to be mentioned that in contrast with a typical liquid–solid two phase system, the gel phase is a microporous material that allows much easier flow and exchange between the sol and gel phases and therefore responds quickly to the demands of reagent for the reaction. In related systems that would contain conventional solid phases with fewer active surfaces than gels, it is expected that the release of reagents would be much slower and this procedure would not be of practical use.

It is envisaged that depending on the ratio of disassembly and reaction rates in the considered system, the reaction would occur either in solution or in the gel phase. Thus, it seems reasonable that for our previous studies with monofunctional amines and flexible diamines,[5] reaction most likely occurred in the gel phase, since assembly of the product appeared in situ. On the contrary, in the present case, the higher solubility of the cyclic product would pull the equilibrium to the solution phase.

4. Experimental section

4.1. General

The NMR experiments were carried out either on a Varian INOVA 500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C) or a Varian MERCURY 300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The FTIR spectra of the gel were measured using a Perkin Elmer 2000 FTIR spectrometer in a KBr cuvette. The ESI-mass spectra were recorded in a Micromass Quattro LC spectrometer equipped with an electrospray ionisation source and a triple quadrupole analyser. A QTOF I (quadrupole–hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface (Micromass, Manchester, UK) was used for HRMS. The drying gas as well as nebulizing gas was nitrogen at a flow of 400 L/h and 80 L/h, respectively. The temperature of the source block was set to 120 °C and the desolvation temperature to 150 °C. A capillary voltage of 3.5 kV was used in the positive scan mode and the cone voltage was set to 20 V. Sample solutions (approx. 5 mg/L) in dichloromethane–methanol (50:50) were infused via a syringe pump directly connected to the interface. Elemental analyses were carried out in a Carlo Erba EA-1108 CHNS analyser.

Molecular mechanics calculations were performed with MACROMODEL 7.0[11] using AMBER* as the force field. An exhaustive conformational search starting from non-folded conformations was performed with the Monte Carlo method by minimisation of 5000 structures using GB/SA simulation of chloroform as the solvent.

4.2. Synthesis

Compound **1** was prepared as previously described.[4]

4.2.1. Compound 3 (1+1). Compound **1** (0.3 g, 0.5 mmol) was dissolved in 100 mL of hot CH_3CN and after few hours a gel was formed. Then, a mixture of (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine (**2**) (103 mg, 0.5 mmol) and Et_3N (140 mL, 1 mmol) in 5 mL of CH_3CN was added on top of the gel. The mixture was slightly shaken by hand (the gel was broken into large jelly fragments) and left at the required temperature overnight. Afterwards, the jelly precipitate was filtered off, washed with base, water and Et_2O and purified by column chromatography (CH_2Cl_2–MeOH). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 0.67 (d, *J*=6 Hz, 6H), 0.73 (d, *J*=7 Hz, 6H), 1.2–1.4 (m, 4H), 1.76 (m, 2H), 2.71 (m, 2H), 3.43 (m, 2H), 3.89 (m, 2H), 4.75 (m, 2H), 6.12 (d, *J*=9 Hz, 2H), 6.91 (m, 6H), 7.0–7.1 (m, 6H), 7.83 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): 18.7, 19.8, 27.9, 32.1, 35.7, 58.8, 59.8, 127.2, 128.0, 128.5, 142.4, 158.0, 172.3; ESI-TOF-MS *m*/*z*=551.3 $[M+H]^+$; elemental analysis calcd for $C_{30}H_{42}N_6O_4$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.15; H, 7.81; N, 15.13.

4.2.2. Compound 4. Compound **4** was prepared from *N*-Cbz-L-valinyl propyl amine[6] (1.45 g, 5.0 mmol) in two consecutive steps. First, the Cbz protecting group was removed by overnight hydrogenation (1 atm) in 60 mL of methanol using 185 mg of 5% Pd/C as catalyst. The catalyst was filtered off through Celite and the solvent removed. The resulting material (0.62 g, 3.9 mmol) was dissolved in dry THF (50 mL) and triethylamine (0.6 mL, 4.3 mmol) was added. To this solution under a nitrogen atmosphere and cooled in an ice bath, 4-nitrophenylchloroformate (0.79 g, 3.9 mmol) in 30 mL of dry THF was added dropwise. The mixture was stirred overnight at room temperature. The solvent was removed and the residue was collected with 50 mL of dichloromethane. The insoluble material was filtered off and after solvent removal the crude was purified by column chromatography using dichloromethane as eluent. The pure compound was obtained as a white solid (0.35 g, 1.1 mmol, overall yield 22%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 0.93 (t, *J*=7 Hz, 3H), 1.01 (d, *J*=7 Hz, 6H), 1.52 (m, 2H), 2.11 (m, 1H), 3.24 (m, 2H), 3.95 (dd, 1H, *J*=9 Hz, 7 Hz, 1H), 5.93 (br, 1H), 6.03 (d, *J*=9 Hz, 1H), 7.30 (d, *J*=9 Hz, 2H), 8.23 (d, *J*=9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 11.6, 18.3, 19.4, 23.0, 31.9, 41.6, 61.1, 122.2, 125.4, 153.5, 170.7. IR (KBr): 1229, 1345, 1638, 1721, 3286 cm^{-1}; ESI-MS *m*/*z*=346.1 $[M+Na]^+$; elemental analysis calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 55.94; H, 6.44; N, 13.12.

Acknowledgements

The authors thank Generalitat Valenciana (Grant GV06/322) for funding.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.02.069.

References and notes

1. (a) *Molecular Gels. Materials with Self-assembled Fibrillar Networks*; Weiss, R. G., Terech, P., Eds.; Springer: Dordrecht, 2006; (b) *Low Molecular Mass Gelators: Design, Self-Assembly, Function*; Fages, F., Ed.; Topics in Current Chemistry Series; Springer: New York, NY, 2005; Vol. 256.
2. (a) Terech, P.; Weiss, R. G. *Chem. Rev.* **1997**, *97*, 3133–3159; (b) van Esch, J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 2263–2266; (c) Estroff, L. A.; Hamilton, A. D. *Chem. Rev.* **2004**, *104*, 1201–1217.
3. Sangeetha, N. M.; Maitra, U. *Chem. Soc. Rev.* **2005**, *34*, 821–836.
4. (a) Love, C. S.; Chechik, V.; Smith, D. K.; Ashworth, I.; Brennan, C. *Chem. Commun.* **2005**, 5647–5649; (b) Shirakawa, M.; Fujita, N.; Shinkai, S. *J. Am. Chem. Soc.* **2005**, *127*, 4164–4165; (c) Dautel, O. J.; Robitzer, M.; Lère-Porte, J.-P.; Serein-Spirau, F.; Moreau, J. J. E. *J. Am. Chem. Soc.* **2006**, *128*, 16213–16223.
5. Miravet, J. F.; Escuder, B. *Org. Lett.* **2005**, *7*, 4791–4794.
6. Gibson, S. E.; Lecci, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1364–1377 and references cited therein.
7. (a) Becerril, J.; Bolte, M.; Burguete, M. I.; Galindo, F.; García-España, E.; Luis, S. V.; Miravet, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 6677–6686 and references cited therein; (b) Blankenstein, J.; Zhu, J. *Eur. J. Org. Chem.* **2005**, 1949–1964; (c) Bru, M.; Alfonso, I.; Burguete, M. I.; Luis, S. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 6155–6159.
8. Escuder, B.; Martí, S.; Miravet, J. F. *Langmuir* **2005**, *21*, 6776–6787.
9. Escuder, B.; Llusar, M.; Miravet, J. F. *J. Org. Chem.* **2006**, *71*, 7747–7752.
10. Fraction of compound **1** in solution was determined to be 10%. See Ref. 3.
11. Mohamadi, F.; Richards, N. G. J.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467.